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PRE-APPEAL BRIEF REQUEST FOR REVIEW		Docket Number (Optional) 88066-7900
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<p>Applicant requests review of the final rejection in the above-identified application. No amendments are being filed with this request.</p> <p>This request is being filed with a notice of appeal.</p> <p>The review is requested for the reason(s) stated on the attached sheet(s). Note: No more than five (5) pages may be provided.</p> <p>I am the</p> <div style="display: flex; justify-content: space-between;"> <div style="width: 45%;"> <input type="checkbox"/> applicant/inventor. <input type="checkbox"/> assignee of record of the entire interest. See 37 CFR 3.71. Statement under 37 CFR 3.73(b) is enclosed. (Form PTO/SB/96) <input checked="" type="checkbox"/> attorney or agent of record. Registration number <u>30,256</u> <input type="checkbox"/> attorney or agent acting under 37 CFR 1.34. Registration number if acting under 37 CFR 1.34 _____ </div> <div style="width: 45%; text-align: center;">  Signature Allan A. Fanucci Typed or printed name 212-294-3311 Telephone number July 26, 2011 Date </div> </div> <p>NOTE: Signatures of all the inventors or assignees of record of the entire interest or their representative(s) are required. Submit multiple forms if more than one signature is required, see below*.</p>		
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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of: Dario Norberto R. CARRARA et al. Confirmation No.: 5916

Application No.: 10/798,111

Group Art Unit: 1616

Filing Date: March 10, 2004

Examiner: Nathan W. Schlientz

For: METHODS AND FORMULATIONS FOR
TRANSDERMAL OR TRANSMUCOSAL
APPLICATION OF ACTIVE AGENTS

Atty. Docket No.: 88066-7900

PRE-APPEAL BRIEF REQUEST FOR REVIEW

Mail Stop : AF

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Sir:

Applicant requests a panel review of the decision of the Examiner mailed April 27, 2011, rejecting claims 1, 3-5, 7, 11, 13, 17-19, 29, 37, 40-42, 46, 56-58, 60-63 and 67-72 of the above-identified application.

The claims were rejected as unpatentable over International Patent Application Publication No. WO 02/22132 to Gray et al. or US Patent No. 7,030,104 ("Gray") in view of US Patent No. 6,503,894 to Dudley et al. ("Dudley"), and an article by Wang et al. (the Journal of Clinical Endocrinology and Metabolism, 2000 ("Wang")).

As disclosed in the application and as explained throughout prosecution, the present invention relates to a formulation containing testosterone as the active agent, or method of use thereof, or a kit containing such a formulation. The formulation of the present invention surprisingly achieves sufficient absorption to result in an effective dosage of testosterone circulating in serum without the inclusion of the long-chain fatty alcohols or and the long-chain fatty acids that have been used to date. This leads to greater patient compliance and greater effectiveness as the formulations are in fact well tolerated when administered. None of these novel features of the presently claimed invention is disclosed or even suggested in the cited references.

Gray relates to a topical hormonal composition comprising as active ingredients, a progestogen derived from 19-nor progesterone and estradiol or one of its derivatives, a vehicle which allows the systemic passage of said active ingredients, chosen from the group constituted by a solubilizing agent, an absorption promoting agent, a film-forming agent, a gelling agent and their mixtures, in combination or in a mixture with suitable excipients for the realization of a gelled and/or film-forming pharmaceutical form.

In contrast, the present claims as amended are specifically directed to a formulation containing testosterone as the active agent, or method of use thereof, or a kit containing such a formulation. Therefore, as acknowledged by the Examiner, Gray does not teach each and every element of the present claims, and the Dudley and Wang references are cited.

Dudley relates to a pharmaceutical composition useful for treating hypogonadism comprising an androgenic or anabolic steroid, a C₁-C₄ alcohol, a penetration enhancer such as isopropyl myristate, and water. Wang discloses packaging hydroalcoholic gels containing 1 wt.% testosterone in a multidose bottle with an actuator pump for treatment of hypogonadal males.

First of all, there is no teaching or suggestion in either reference to motivate a person of ordinary skill in the art to replace the active agents in the composition of Gray, i.e., progestogen derived from 19-nor progesterone and estradiol or one of its derivatives, with an androgenic or anabolic steroid such as testosterone that is disclosed in Dudley. Importantly, Gray is specific for cutaneous topical preparations containing a synthetic progestogen and a natural or synthetic estrogen. Therefore, a person of ordinary skill in the art, following the teachings of Gray, will not choose to replace its active agents with testosterone mentioned by Dudley as these active agents are used for entirely different treatments.

The Examiner disagrees with this statement and instead suggests on page 6 of the office action that it would well be within the purview of a skilled artisan to use testosterone in the formulations of Gray. There is nothing in Gray or the other references that suggests such a substitution to a skilled artisan. Assuming, *arguendo*, that this substitution would be considered by a skilled artisan, it then becomes necessary to consider in which of the numerous formulations of Gray would testosterone be substituted in place of the active agents taught by Gray.

In the final office action, the Examiner cites a portion of Table I of Gray, but conveniently leaves out more than half of that table. While formulations G29-287, G29-299 and Tx11323 batch 12 have some similar solvents to what are included in the presently claimed formulations, there is

no disclosure even in those examples of any relationships or amounts for those components to arrive at what is presently claimed. The formulations that were omitted from the office action reproduction of Table 1, however, do not include the recited components or amounts that are set forth in the present claims.

In addition, Applicant recites a preferred ratio for the polyalcohol and permeation enhancer (i.e., the monoalkyl ether of diethylene glycol) of from 2:1 to 1:1. Although using a different permeation enhancer, three of the omitted formulations in Gray teach a ratio of 2.67:1 (i.e., 8:3), a ratio that is outside of the presently claimed range. The testing of those formulations leads Gray to conclude in column 12, lines 43-56 that when nomegestrol acetate is combined with estradiol, a promoter effect of estradiol on the diffusion of nomegestrol acetate was found using two pairs of different solvents: the propylene-glycol/Transcutol pair (Table 3) and the propylene glycol/Solketal pair (Table 4). This teaches a skilled artisan that either formulation is suitable for obtaining the promoter effect.

Gray then goes on to present in vivo and in vitro test results in Column 13 and concludes that, to ensure a complete therapeutic effect in all women, it would be worthwhile to obtain even higher circulating levels of nomegestrol acetate and that the results of diffusion in vitro were improved by other formulations (see Gray at col. 13, lines 40-45). Gray then prepares a new series of gels based on the formulation of Table 7, which does not include a permeation enhancer of a monoalkyl ether of diethylene glycol and which has a ratio of propylene glycol to permeation enhancer (i.e., absorption promoter) above 2:1 and in particular 2.67:1 (8:3). As discussed by Gray in col. 16, lines 20 to 56, the best results were found with formulations G9-100, G49-106, G49-108 and G42-120. The absorption promoters (or permeation enhancers) used for those formulations are octanoic acid, octadec-9-enoic acid, dodecanoic acid and solketal, i.e., (2,2-dimethyl-1,3-dioxolan-4-yl)methanol, respectively. Thus, even if testosterone is substituted for nomegestrol acetate and estradiol in these formulations, none would fall within the present claims.

Gray furthermore observed that the first three formulations contain absorption promoters that are "badly tolerated" by the skin such that those formulations "must be used with caution" (*id.* at col. 16, lines 29-30). Based on that he concludes that formulation G42-120 is the most preferred.

Accordingly, it is respectfully submitted that a skilled artisan, following the reasoning in the final office action, would not be led to the formulations of Table 1, but instead might be taught to substitute testosterone into the G42-120 formulation which provided the best performance and

safety. As noted above, this formulation does not use a permeation enhancer of a monoalkyl ether of diethylene glycol and does not include a ratio of propylene glycol to permeation enhancer of 2:1 to 1:1. The other three formulations that provided the best results are also not covered by the present claims as the fatty acids are specifically excluded by the present claims in order to avoid undesirable odor and irritation from such compounds during use of the formulation. Thus, a fair reading of the entire Gray reference by a skilled artisan does not lead to a formulation according to the present claims. Applicants submit that this demonstrates reversible error in the rejection.

And in addition, a skilled artisan would have no expectation of success to replace progesterone and estradiol taught in Gray with testosterone disclosed in Dudley. As mentioned above, these are different active agents that perform differently even if used with similar solvents. As supported by a research paper submitted during prosecution (P. Karande et al., *High Throughput Screening of Transdermal Formulations*, *Pharmaceutical Research*, vol. 19, no. 5, May 2002, pp. 655-660), more than 200 chemical enhancers including surfactants, fatty acids, fatty alcohols, and organic solvents have been used in attempts to increase transdermal drug transport and generally testing is needed to determine which are the most suitable for a particular active.

The presently claimed invention is also distinguishable from Gray in that Gray's disclosure is clearly directed at combinations of actives where one is used to favor the diffusion of one of the actives over the other. In contrast, the present claims are directed to a single active, testosterone.

The combination of Gray and Dudley fails to obtain the present claims for additional reason. Even ignoring the fact that Dudley does not specifically disclose, teach or even mention that testosterone could or should be substituted for progesterone derived from 19-nor progesterone and estradiol or one of its derivatives in Gray's formulation, Dudley also prefers to use solvents that are not covered by or obvious variations of those that are recited in the present claims. Dudley prefers to use fatty acid derivatives, and in particular, isopropyl myristate, for his testosterone formulations (see the AndroGel® formulation in Table 5 of Dudley). Even though Dudley does mention other compounds such as diethylene glycol monomethyl ether in his listing of permeation enhancers, he attributes no preference to that compound. Thus, one of ordinary skill in the art, reading Dudley, will not be taught or motivated to select diethylene glycol monomethyl ether as taught in Gray in place of isopropyl myristate as the transdermal enhancer for the active agent testosterone as presently claimed. And as Gray does not prefer diethylene glycol monoethyl ether as an absorption agent, there is no motivation to use that enhancer from Dudley as he does not even mention it in his

listing of useful permeation enhancers. Even if he did, there are so many mentioned that a skilled artisan would need to conduct extensive testing before coming up with the present values, and even there one would expect similar performance to what Gray discloses rather than the improved performance of the formulation of the present invention. Thus, claims 7, 42, 60-63 and 68-72 are further distinguishable from the cited references.

Accordingly, the compositions of Gray and Dudley cannot be combined as suggested by the Examiner except by relying on the disclosure of the present application and performing a hindsight analysis of the claims. In fact, the formulations of Gray and Dudley include additional permeation components of the types that are excluded from the present claims, e.g., fatty compounds, and others so that it is certainly not clear as to how a skilled artisan could come up with the present formulations. Furthermore, since there is no teaching in Gray or Dudley to lead a skilled artisan to the presently claimed formulations, the rejection can only be based on a selectively picking and choosing of the prior art ingredients using the present specification as a guide. The determination of obviousness is not whether a person could, with full knowledge of the present invention, reproduce it from prior art. The question is whether there would be some teaching, suggestion, or motivation in the art to do so. This judgment cannot be made with the benefit of hindsight and Applicant submits that it is improper to take isolated disclosures from other formulations and change them in light of the now-known template of the present application, unless there is some direction in the prior art that would suggest this or that would clearly motivate a skilled artisan to do so. As no such motivation, teaching or suggestion exists in the cited references, the presently claimed invention is not obvious in view of Gray and/or Dudley and/or Wang. In fact, Wang apparently is cited for his disclosure of a container, but this does not modify the formulations of Gray or Dudley to arrive at Applicant's claims. As the cited references, either alone or in combination, do not teach or suggest the presently claimed formulation, they do not render the present claims obvious.

Based on the foregoing, Applicant submits that reversible error has been demonstrated.

Respectfully submitted,



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